SEPARATING CONTRIBUTIONS OF PREFRONTAL CORTEX SUBREGIONS TO AGE-RELATED ASSOCIATIVE MEMORY IMPAIRMENTS

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SEPARATING CONTRIBUTIONS OF PREFRONTAL CORTEX SUBREGIONS TO AGE-RELATED ASSOCIATIVE MEMORY IMPAIRMENTS

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SUMMARY

The anterior prefrontal cortex (aPFC) is believed to play a critical role in integrating the outputs of lower-order processes, such as evaluations of item or inter-item properties. The high-order integration functions attributed to the aPFC have been shown to support complex reasoning. but the region's role in episodic encoding is less well understood. Emerging data suggest high-order PFC functions may be particularly susceptible to the effects of age and may contribute to older adults' associative memory impairments. It is currently unknown how aging interferes with aPFC operations necessary for integrating multiple relations for episodic encoding and retrieval. We investigated this issue in the current fMRI study. Young and older adults were presented with an occupation and an object and were asked to judge how likely the two were to interact, either in general or within the context of a given scene. When provided with a scene, participants needed to consider and integrate the distinct relations between the three items to reach a decision: a task dependent on aPFC functions. fMRI data were collected during encoding, and memory for object-occupation pairings and their associated contexts was tested outside of the scanner. fMRI results showed greater left DLPFC activity with increasing integration demands for both young and older adults. Older adults exhibited memory impairments for both the pairs and contexts, despite similar engagement of aPFC regions as the young. This could indicate that integration processes were intact yet inefficient in older adults. Alternatively, performance deficits may have resulted from age-related differences in whole-brain patterns of task-related encoding activity.

CHAPTER 1. INTRODUCTION

An inevitable aspect of growing older is the decline of various cognitive functions (F. I. Craik & Bialystok, 2006). While factors such as physical activity and social support are associated with slower rates of decline (Barulli & Stern, 2013), even healthy older individuals who are free of age-related pathology experience some degree of limitation on a number of mental abilities (Lindenberger, 2014). Perhaps taking the hardest hit of these cognitive functions is episodic memory, associative memory in particular. Indeed, across numerous studies, older adults consistently perform worse on tasks that assess this particular type of memory (Old & Naveh-Benjamin, 2008). Associative memory governs our ability to bind and retrieve associations between people, events, and objects, allowing us to distinguish one event from another.

While we have all experienced difficulties learning names or locating misplaced items, young adults generally have the luxury of attributing such difficulties to simple absentmindedness or lack of effort at encoding. Older adults, on the other hand, are much more likely to feel a sense of distress in the wake of such memory failures, perhaps due to the fact that these are often early signs of Alzheimer's disease (Bolla, Lindgren, Bonaccorsy, & Bleecker, 1991). Because the prefrontal cortex (PFC) plays a critical role in associative memory, it is often the focus of investigations into age-related associative memory impairments (Raz, 2000; West, 1996).

1.1 Neuroscientific Theories of Aging

Offering a rationalization for the functional decline that accompanies aging is the highly influential "frontal aging hypothesis," which posits that the PFC is particularly vulnerable to age-related deterioration and that functions largely dependent upon this region will show the greatest decline (Greenwood, 2000; West, 1996). Consistent with this hypothesis are various studies showing declines in white and gray matter volume that are disproportionately greater within the PFC compared to other neural regions (Nyberg et al., 2010; Raz et al., 1997; Raz & Kennedy, 2009), positive associations between PFC volume and associative memory accuracy in the elderly (Becker et al., 2015), and age-related reductions in PFC activity, both during encoding (Dennis et al., 2008; Dulas & Duarte, 2011) and retrieval (Duarte, Henson, & Graham, 2008; Dulas & Duarte, 2012; McDonough & Gallo, 2013). Notably, reductions in PFC activity during tests of memory have been shown to occur despite age-equivalent recruitment of medial temporal lobes (MTL) (Dulas & Duarte, 2012; Morcom, Li, & Rugg, 2007). The MTL includes the hippocampus and parahippocampus, and is part of the larger "core episodic network" (Benoit & Schacter, 2015). This network has been implicated in the process of binding various details of complex events into a whole, integrated memory trace, which allows for accurate retrieval of encoded associations (Eichenbaum, Yonelinas, & Ranganath, 2007; Johnson, Hashtroudi, & Lindsay, 1993). While dysfunctional MTL processes sometimes contribute to associative memory impairments (Cansino et al., 2015), evidence suggests this may not be a major contributing factor until healthy older adults reach the eighth or ninth decade of their lives (Salami, Eriksson, & Nyberg, 2012).

Other theories of aging lend support to the idea of age-related dysfunctional PFC processes having a greater impact on associative memory impairments than MTL

dysfunction. The "associative deficit hypothesis" posits that such impairments are the result of failures to create associations between items, or failures to retrieve these associations at a later time (Naveh-Benjamin, 2000). Another exceedingly influential model, the "inhibitory deficit hypothesis", suggests that cognitive impairments result from increased interference due to older adults' difficulty in "tuning out" or inhibiting goal- or task-irrelevant information (Hasher & Zacks, 1988). While the associative deficit, inhibitory deficit, and frontal aging hypotheses offer distinct possibilities to explain age-related decline, they should not be viewed as mutually exclusive. Deterioration in PFC regions conceivably could lead to decreased attentional control, which impairs the ability to encode and retrieve information – an ability that is critical for optimal associative memory performance.

Given the size and functional diversity of the PFC, it seems the frontal aging hypothesis misses critical intricacies when describing a generalized decline in global functioning of PFC-mediated processes. These processes include attention, decision-making, and top-down modulation. Collectively, PFC-dependent operations are termed *cognitive control* processes, or *executive functions*. Executive functions allow for flexible behavioral responses in light of processed information, allowing for the execution of actions that advance one toward his or her current task goals (Miller & Cohen, 2001). As it is, the frontal aging hypothesis falls short in making predictions regarding various regions within the PFC and their associated functions that underlie cognitive impairments that accompany old age. The goal of the proposed study is to elucidate potential causes of age-related associative memory impairments by investigating the effects of age on specific PFC subregions, their extended functional networks, and the behavioral functions they support.

1.2 Hierarchical Organization of the PFC

Functional magnetic resonance imaging (fMRI) provides powerful, non-invasive measures of brain functioning during cognitive tasks by measuring hemodynamic correlates of neural activity. This imaging technique can provide critical insight into the mechanisms underlying PFC functioning and how these functions might be impaired in older adults. Patient and neuroimaging work has shed light on the separation of cognitive control between the two hemispheres and along rostral-caudal and dorsal-ventral gradients (Badre, 2008). Organization along these gradients creates a hierarchical model, with each region contributing to various processing strategies, based on current task-goals (Christoff & Gabrieli, 2000). The left ventrolateral PFC (VLPFC; inferior frontal gyrus/ Brodmann area [BA] 44/45/47) is associated with "first-order" processes, such as selection of relevant concrete item properties (e.g., "What is the color of this object?"). Not only do these processes select item features from the environment by directing attention toward task-relevant information (Blumenfeld & Ranganath, 2007), but they are also involved in the selection of item representations from memory and the resolution of interference during retrieval (Wais, Kim, & Gazzaley, 2012). The left dorsolateral PFC (DLPFC; middle frontal gyrus/ BA 9/46) has been tied to "second-order" processes (Badre, 2008), such as evaluation of concrete inter-item properties or event details (e.g., "Are these two objects the same color?"), and tends to be insensitive to integration demands. Bilateral rostrolateral PFC (RLPFC; BA 10 and rostral BA 46) has been suggested to control "highest-order" processes (Badre & D'Esposito, 2007). An example of this is relational integration, or the joint consideration and combination of multiple

relations (e.g., “Is your decision about the first pair of objects the same as your decision about the second pair of objects?”).

When relationships between items are evaluated, both externally- and internally-generated details are processed. Internally-, or self-, generated information is that which must be inferred, as it cannot be directly perceived from the environment. According to Christoff and Gabrieli’s (2000) hierarchical model of PFC organization, the VLPFC and DLPFC are active during the evaluation of externally-generated information. Evaluation of internally-generated information is a bit more taxing, and therefore requires additional recruitment of the RLPFC (Christoff & Gabrieli, 2000; Christoff, Ream, Geddes, & Gabrieli, 2003). The ability to generate inferences regarding relations between items that have not been explicitly compared is critical for deductive reasoning. This type of reasoning allows us to accomplish many of the complex cognitive tasks encountered in everyday life, such as action planning. For example, say you have a doctor’s appointment at 9:00 AM and you know the commute takes half an hour. You can reason that if you leave at 8:30 AM, you will arrive at the doctor’s office on time for the appointment.

1.3 RLPFC Functions

Increasing the number of relations that must be combined in order to arrive at the correct conclusion places greater demands on the RLPFC. For instance, Raven’s Progressive Matrices have been shown to reliably increase RLPFC activation when participants need to consider two relational changes in order to select the correct target, compared to when the target varied only along one dimension (Christoff et al., 2001). Similarly, on transitive inference paradigms, the RLPFC is more active during integration

of associations between two pairs of items than during simple comparison of two items. This is true of items in the visuospatial (Wendelken & Bunge, 2010) and verbal/ semantic domains (Bunge, Wendelken, Badre, & Wagner, 2005). Verbal analogical reasoning, which is especially critical for learning and abstract thought, relies on our ability to retrieve semantic relations from long term memory, as well as our ability to integrate across the retrieved relations. The RLPFC has been suggested to utilize representations of mental semantic relations relayed from the hippocampus, (Wendelken & Bunge, 2010), and it keeps these distinct retrieved relations active for the purpose of jointly considering, comparing, and linking them into an integrated representation (Bunge et al., 2005) to be stored in memory for later retrieval.

Given the evidence of RLPFC operations in both semantic and visuospatial relational integration, Wendelken, Chung, and Bunge (2012) investigated whether the processes functioned in a domain-general manner or if some form of dorsal-ventral gradient existed within the RLPFC, with dorsal regions contributing more to visuospatial integration than semantic integration. They tested these competing hypotheses using a relational matching task in each of these domains. Participants judged either the similarity of items in a pair or the similarity of relations between two pairs of items. fMRI results indicated great overlap within the RLPFC for semantic and visuospatial processing of item similarity. For the processing of relational similarity, researchers observed systematic differences in loci of activation peaks as a result of differences in input, suggesting non-uniform distributions of cells involved in visuospatial and semantic integration. Authors proposed that a neuron's anatomical location determines the type of information it receives, with those located more ventrally in left RLPFC having privileged access to inter-item semantic information

relayed from the left VLPFC, and those located more dorsally having privileged access to inter-item visuospatial information relayed from the superior frontal sulcus and DLPFC. Thus, neurons in the RLPFC are believed to operate in a domain-general manner, but exhibit domain-sensitivity as a result of a dorsal-ventral gradient (Wendelken, Chung, & Bunge, 2012).

RLPFC-mediated processes may not be limited to the initial processing of information. Many researchers have indicated RLPFC involvement in various aspects of episodic memory, including specification of strategies to recover contextual details from past experiences and monitoring of retrieved content (Dobbins & Wagner, 2005; see Westphal, Reggente, Ito, & Rissman, 2016 for review). Dobbins and Wagner (2005) proposed that the RLPFC promotes the intermediate integration of recovered information with a final decision criterion. Reynolds and colleagues (2006) investigated whether the processes recruited by the RLPFC for episodic retrieval are distinct from those recruited for integration. fMRI data revealed one subregion that showed unique sensitivity to integration demands and another that showed joint sensitivity to retrieval and integration demands. Authors suggested that the RLPFC does not perform retrieval-specific operations, but rather employs more general operations that function to integrate the results of central and ancillary retrieval processes (Reynolds, McDermott, & Braver, 2006).

1.4 Relational Integration and Aging

Given these findings, it is surprising that the research on age-related changes in this particular PFC subregion is severely limited. It is well known that general reasoning ability becomes increasingly impaired as we grow older (Salthouse, 1992), but this ability is

particularly challenged in the face of tasks requiring the manipulation and integration of multiple details to generate novel inferences (Viskontas, Holyoak, & Knowlton, 2005). The increased difficulty in reasoning may be directly tied to age-related working memory deficits, whether that be limitations on storage capacity and attentional resources (F. Craik & Byrd, 1982), problems ignoring irrelevant information (Hasher & Zacks, 1988), or decreases in processing speed (Salthouse & Babcock, 1991).

Recently, Bugaiska and Thibaut (2015) compared the latter two of these possibilities directly using an analogical reasoning task where they manipulated the complexity of the task by varying the semantic relatedness of word pairs and the number of distractors presented in the display. Young adults were compared to older adults (age range: 61-71, mean: 63) and a group of "old-old" adults (age range: 72-96, mean: 78). While both inhibition capabilities and processing speed showed clear decrements with age, processing speed accounted for significantly more age-related variance in performance in the younger group of old adults. In the older group, however, both processing speed and inhibition explained the performance differences (Bugaiska & Thibaut, 2015). Authors suggest that increasingly complex relational tasks require more time to compare and combine the relations. Due to the temporal restrictions of working memory, we are essentially racing the clock to reach a final decision before the information fades from our mental workspace. If the processes used to perform these operations are inefficient, the relations may be integrated incorrectly, resulting in an incomplete memory trace. Additionally, given the findings of Reynolds and colleagues (2006), if the integration operations are deficient, then the retrieval operations should also be impaired.

Few studies have investigated the effects of aging on RLPFC recruitment, and none, to our knowledge have assessed these effects in relational integration. Our lab incidentally found evidence that contrasted RLPFC with VLPFC and DLPFC function in a study that tested methods to improve source memory accuracy and reduce age-related deficits by directing participants' attention to item-source associations during encoding. While source memory performance improved for both groups, age-related differences endured. Dulas and Duarte (2014) suggested these differences could be attributed to increased recruitment of rostromedial PFC and under-recruitment of RLPFC in older adults. The two areas are thought to reflect self-referential and relational processes, respectively. Older adults were able to recruit VLPFC and DLPFC processes during associative memory encoding and retrieval, but exhibited impaired recruitment of RLPFC processes. In this design, relational integration demands were not explicitly manipulated, so the exact nature of RLPFC involvement can only be inferred.

It is currently unknown how aging affects the RLPFC's ability to integrate and encode multiple relations for later associative retrieval. The goal of the proposed study is to specify the neurocognitive components of control mediated by the RLPFC and to elucidate how age-related dysfunction of these processes contributes to associative memory impairments. We predict behavioral results will reflect typical patterns of aging on memory, with young adults exhibiting better overall memory performance than older adults. Specifically, we anticipate that young adults will demonstrate similar memory for trials involving one relation and those requiring integration of multiple relations. Older adults, on the other hand, are expected to remember more trials that do not require integration than trials that do require this additional processing. We predict left DLPFC

will support inter-item associative encoding but not integration, in both young and older adults. RLPFC activity is expected to be greater for integration of multiple relations than inter-item comparisons, though these differences in activation for the two tasks may be reduced in older adults if their ability to integrate is impaired as a result of reduced RLPFC recruitment.

CHAPTER 2. METHOD

2.1 Participants

Participants were 31 young adults, ages 18-33, and 30 older adults, ages 61-77, recruited from Georgia Institute of Technology and the Atlanta community. Groups did not significantly differ in gender [$\chi^2(1, N = 61) = .014$, $p = .906$], but older adults had about 1.4 more years of education than the young [$t(44.43) = 2.35$, $p = .023$]. Group characteristics may be seen in Table 1. Two additional young adults were excluded: one due to claustrophobia and the other due to limited encoding responses. All participants were fMRI eligible, native English speakers, with normal or corrected to normal vision, and with no reports of psychiatric or neurological disorders, vascular disease, psychoactive drug use, or use of CNS-active or antihypertensive medications. One left-handed and one ambidextrous young adult made it through screening due to human error. Analyses were run with and without these individuals and because their data did not seem to make a difference, they were included in the final analyses. All other participants were right-handed. Participation was compensated with class credit or $15 per hour, plus an additional $5 for travel expenses. All participants signed consent forms approved by the Georgia Institute of Technology Institutional Review Board.

Table 1 Group characteristics

Measure	Young (n = 31)	Old (n = 30)
Age	22.45 (3.67)	66.63 (4.32)
Sex (F/M)	17/14	16/14
Education	14.97 (1.56)	16.37 (2.87)
Similarities	14.81 (2.82)	13.17 (3.93)
Visual Puzzles	12.52 (3.24)	12.53 (3.66)

Note. Standard deviations in parentheses. WAIS subtest scores reported as scaled scores.

2.2 Neuropsychological Assessment – WAIS Subtests

After completing the fMRI and behavioral components of the study, participants were administered the Similarities and Visual Puzzles subtests from the *Wechsler Adult Intelligence Scale – Fourth Edition* (Wechsler, 2008a) to provide additional measures of semantic and visuospatial reasoning. Similarities is a subtest of the verbal comprehension index, measuring verbal concept formation, semantic and abstract reasoning, memory, and associative and categorical thinking, among other abilities. In the task, participants were presented with two words representing common objects or concepts (e.g., *piano* and *drum*; *acceptance* and *denial*) and were asked to describe how the words are similar. Fifteen word pairs were presented one at a time, with no given time limit, and corrective feedback was provided for incorrect responses to the sample and first two test items. Visual Puzzles is a subtest of the perceptual reasoning index; it measures a number of abilities, including nonverbal reasoning, ability to analyze and integrate abstract visual stimuli, simultaneous processing, and the ability to anticipate relationships among parts. Within a time-limit of 20-30 s for each item, participants viewed 22 completed puzzles and were asked to select three of the six options that could be combined to create the puzzle (Wechsler, 2008b).

Both tasks were discontinued after three consecutive scores of zero. Raw performance scores were scaled to a metric with a mean of ten and a standard deviation of three to represent an individual's performance relative to his or her same age peers. All participants were within the normal range for their age group. Mean scores can be seen in Table 1.

2.3 Materials

Two hundred sixty unique images were used as stimuli. All images depicted a single, namable object presented in color on a white background. Images were acquired from the Hemera Technologies Photo-Objects DVDs and from Google. Each object image was presented on the screen just above a word indicating a unique occupation. Half of the encoding trials presented the occupation-object pair following a word representing a scene (*integrative trials* hereafter) and the other half presented the pair following a placeholder (*non-integrative trials* hereafter). Forty-two different scenes were used an approximately equal number of times across the Integrative trials.

2.4 Design and Procedure

The study was divided into three main stages: encoding, pair retrieval, and context retrieval. fMRI data was collected only during encoding. Before beginning each stage of the experiment, participants were guided through instructions, which were presented orally by the experimenter and in text on the screen. For encoding, participants were then walked through four example trials before completing a short set of practice trials on their own, though the experimenter provided feedback when necessary. This served to familiarize participants with the procedure and ensure they could sufficiently perform the task before entering the scanner. Practice was repeated as necessary until clear understanding was

demonstrated. The two retrieval stages also included instructions and practice trials, but no example trials. Figure 1 presents the experimental design.

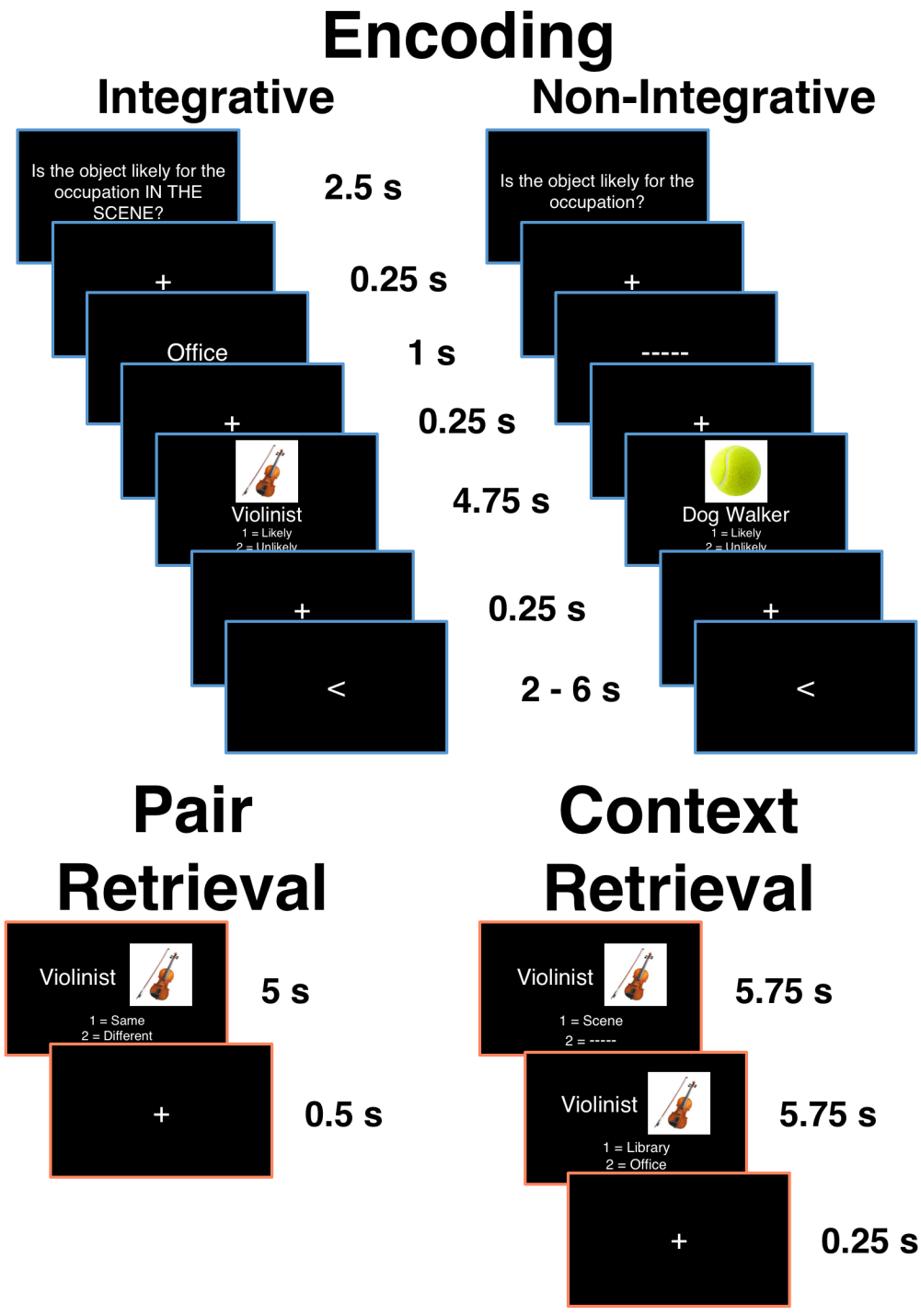

Figure 1 Experimental design

2.4.1 Encoding

The encoding stage was divided into four blocks, each consisting of 63 trials. Each trial began with the presentation a context, either a scene or placeholder (i.e., "-----"), followed by a brief fixation, then an occupation-object pair was displayed. Participants were asked to make a judgment about the likelihood of an interaction between the presented stimuli. For non-integrative trials, participants simply had to determine whether a person with the given occupation would interact with the associated object. For integrative trials, participants made a similar decision regarding the occupation-object pair, only this time, the decision had to be made within the context of the given scene. Therefore, integrative trials required that participants jointly consider the scene-occupation, scene-object, and occupation-object relations, which was emphasized in the task instructions. *Likely* interaction judgments were made by pressing "1" on the number pad, and *unlikely* interaction judgments were made by pressing "2".

To minimize task switching, integrative and non-integrative trials were presented in mini-blocks, where 7-8 trials of each type were presented consecutively. At the beginning of each mini-block, a prompt was shown to inform participants that they should judge the likelihood of the occupation-object interaction either in isolation or within the context of the given scene. Each encoding block began with an integrative mini-block, followed by a non-integrative mini-block, and so on – always alternating between the two conditions. Once the occupation-object pair disappeared from the screen, a fixation cross appeared briefly to signal the beginning of the arrow task. The arrow task maximizes design efficiency by pseudorandomly interspersing event trials with "active" baseline trials lasting between 2 and 6 s, jittered in increments of 2 s (Dale, 1999). Every 2 s, an arrow appeared

on the screen and participants were asked to respond using the number pad to indicate the direction of the arrow: "1" for a left-pointing arrow and "2" for a right-pointing arrow. Requiring participants to respond to the arrows kept them engaged in the task and minimized default mode network activity (Stark & Squire, 2001).

Integrative and non-integrative trials were equally represented across the four encoding blocks. Both trial types were designed to present half of their respective trials as likely interactions and half as unlikely interactions. Integrative unlikely trials were designed so that an equal number presented an unlikely scene-occupation pair, an unlikely scene-object pair, and an unlikely occupation-object pair. Initial behavioral piloting ensured that the design produced high (greater than 80%) agreement between the intended answers and the responses provided by these pilot participants. Percentage of agreement was used to check that participants were performing the task as intended.

2.4.2 Reasoning Task

After the four encoding blocks were completed, participants performed an additional semantic reasoning task before exiting the scanner. This additional task aided in validating the distinct neural regions involved in integration. Using a procedure similar to that used by Bunge and colleagues (2005), we presented participants with two pairs of words, separated by a cue that signaled the task to be performed. For the analogy task, participants evaluated whether the second pair of words was semantically analogous to the first pair. For the semantic relation task, participants determined whether the words in each pair were semantically related. All word pairs were acquired and modified from official SAT practice test analogy questions (College Entrance Examination Board, 2004, 2005).

The experimental design for the reasoning task is presented in Figure 2. Instructions and practice were provided prior to entering the scanner, following the encoding practice. Practice trials were repeated, though not scanned, prior to starting the task. The reasoning task was also mini-blocked and an informative prompt was presented before switching from analogy to semantic, or vice versa. The 10 mini-blocks each contained six trials, for a total count of 60 (30 analogy, 30 semantic). Trials were jittered using the arrow task described above.

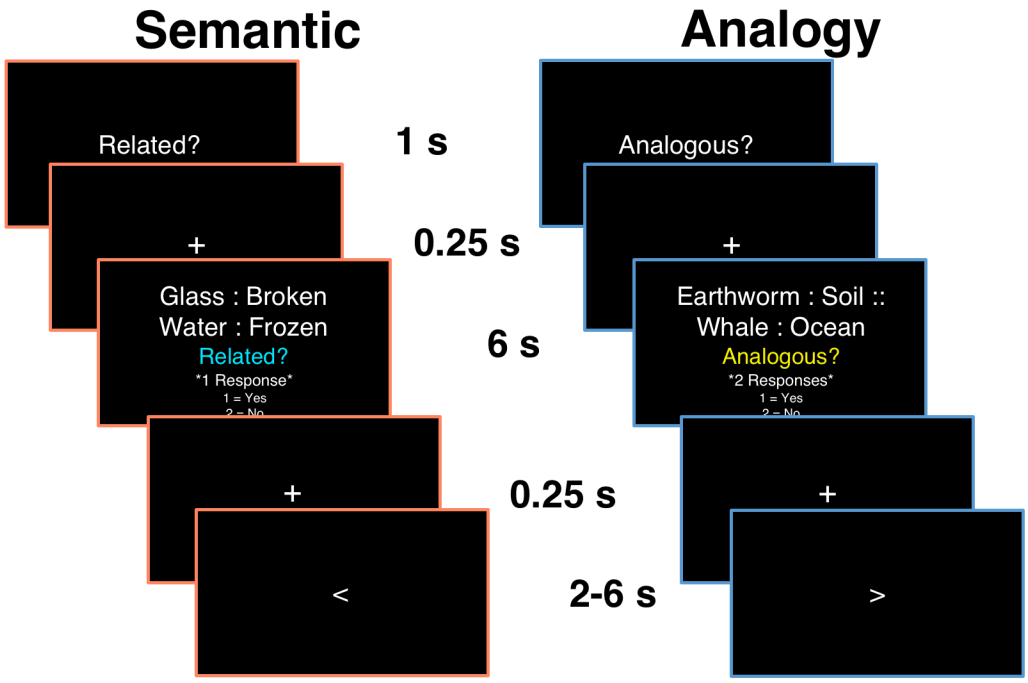

Figure 2 Reasoning task experimental design

2.4.3 Questionnaire

After participants exited the scanner, they were asked to complete a short questionnaire before beginning retrieval. This questionnaire was administered to obtain

information about participants' approach to the task; for example, whether they were visualizing the scenes or generating their own scenes for non-integrative trials.

2.4.4 Pair Retrieval

Similar to encoding, this task was divided into four blocks with 63 trials in each. Participants were presented with an occupation-object pair and were instructed to determine whether the pair was intact (i.e., the occupation is presented with the same object with which it was paired during encoding) or rearranged (i.e., the occupation is presented with a different object). Intact responses were made by pressing "1" and rearranged responses were made by pressing "2". Two of every three occupation-object pairs appeared as intact, and this was counterbalanced across participants; each occupation and object was presented as an intact pair twice and as a rearranged pair once, thereby creating three different counterbalances.

Due to low miss rates in piloting, the orientation of the occupation and object was rotated 90° from the encoding presentation; at retrieval, the occupation appeared to the right (for counterbalance A and C) or left (for counterbalance B) of the object. When the pair is learned during encoding, it is possible for the two elements to become unitized and later remembered as a function of familiarity-based item recognition (Diana, Yonelinas, & Ranganath, 2008). By changing the orientation, the pair cannot be recognized purely on the basis of visuospatial unitization.

2.4.5 Context Retrieval

Following pair retrieval, participants completed an additional memory test to assess success of encoding the context and the pair as an integrated whole. Only intact pairs were tested, as rearranged pairs were associated with two different encoding contexts. The task divided into four blocks, with 42 trials in each, for a total of 168 trials. The occupation-object pair was presented and participants were first asked to determine whether the pair was presented following a scene or the placeholder, by pressing "1" or "2", respectively. If they selected the first option, a new question appeared asking them to select the correct scene from two options. If the placeholder was selected in the first question, the second question was not asked.

For all behavioral analyses, significant interactions at an alpha (α) level of .05 were followed up with subsidiary ANOVAs and *t*-tests to determine the source of the effects. Where appropriate, reported *p*-values were corrected using Huyhn-Feldt corrections.

2.5 fMRI Acquisition

Scanning was performed on a 3T Siemens TIM Trio system at the Center for Advanced Brain Imaging. Functional data was acquired using a gradient echo pulse sequence (37 transverse slices oriented along the anterior-posterior commissural axis with a 30 degree upward tilt to avoid the eyes, repetition time of 2 s, echo time of 30 ms, 3×3×3.5 mm voxels, 0.8 mm interslice gap). Four encoding blocks of 345 volumes were acquired, as well as a block of 323 volumes for the reasoning task. The first 2 volumes of each block were discarded to allow for equilibration effects. A high-resolution T1- weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) image was collected for normalization.

2.6 fMRI Analysis

2.6.1 Preprocessing

Data were preprocessed and analyzed via SPM12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were corrected for differences in slice timing acquisition using the middle slice of each volume as the reference, spatially realigned and resliced with respect to the first volume of the first block. Each participant's MPRAGE scan was coregistered to the mean EPI image, produced from spatial realignment. Each coregistered structural scan was then segmented using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) SPM12 toolbox (Ashburner, 2007). DARTEL is a suite of tools fully integrated with SPM12, which the SPM12 manual recommends over optimized normalization, to achieve sharper nonlinear registration, for intersubject alignment. This method also achieves better localization of fMRI activations in Montreal Neurological Institute [MNI] space. This method has been used successfully in several previous studies with various healthy and neurological populations (Pereira et al., 2010; Yassa & Stark, 2009). Briefly, the gray and white matter segmented images were used to create a study-specific template using the DARTEL toolbox and the flow fields containing the deformation parameters to this template for each subject were used to normalize each participant's realigned and resliced EPIs to MNI space. Normalized EPI images were written to 3 × 3 × 3 mm and smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel. The EPI data were then high-pass filtered to a minimum of 1/128 Hz and grand mean scaled to 100.

2.6.2 Statistical Analyses

Statistical analysis was performed in two stages. First, neural activity was modeled as a series of 4 s epochs at study (i.e., delta functions) of the various event types (e.g., integrative intact, non-integrative rearranged) and convolved with a canonical hemodynamic response function. The time courses were then down-sampled to the middle slice to form the covariates for the General Linear Model. For each participant and block, six covariates representing residual movement-related artifacts, determined by the spatial realignment step, were included in the first-level model to capture residual (linear) movement artifacts. Voxel-wise parameter estimates for these covariates were obtained by restricted maximum-likelihood estimation, using a temporal high-pass filter (cutoff 128 s) to remove low-frequency drifts and modeling temporal autocorrelation across scans with an AR(1) process.

Contrasts of the parameter estimates for each participant were submitted to the second stage of analysis (treating participants as a random-effect). Mixed ANOVA models were created for the study period that allowed us to examine both within-group effects and group interactions. Because rearranged pairs contained multiple encoding events, they were not included in the ANOVA.

2.6.2.1 Subsequent Memory for Occupation-Object Pairs

To assess subsequent memory effects, a 2 × 2 × 2 model included factors of condition (integrative, non-integrative), pair accuracy (hit, miss), and group (young, old). Ten participants (five young, five old) had an insufficient number of misses and could therefore not be included in this model.

2.6.2.2 Integration Demands

To examine integration effects, a 3 x 2 model included factors of condition (integrative pair + context, integrative pair – context, non-integrative pair hit) and group (young, old). Note that *integrative pair + context* indicates trials where both the pair and context were subsequently remembered correctly, and *integrative pair – context* indicates trials where the pair was subsequently remembered but the context was forgotten. Three older adults were not included in this model, as they had an insufficient number of context hits.

2.6.2.3 Effects of Likeliness Judgments

To examine effects of likeliness judgments (i.e., likely/unlikely responses provided at encoding), a 2 x 2 x 2 model included factors of condition (integrative, non-integrative), response (likely, unlikely) and group (young, old). Only subsequent hits were used, as there were too few miss trials to split into likely and unlikely misses. Twelve participants (six young, six old) had an insufficient number of unlikely hits and could therefore not be included in this model.

2.6.2.4 Reasoning Task

Finally, the reasoning task was analyzed with a 2 x 2 model that included factors of task type (analogy, semantic) and group (young, old). Only correct trials were included in this model, as a majority of participants had too few incorrect trials. Three participants (one young, two old) did not complete the task due to time constraints, one young adult had excessive movement, and 11 participants (one young, ten old) did not perform the task correctly, often due to providing only one response for semantic trials.

Covariates modeling the mean across conditions for each participant were also added to each model for all contrasts in the second-level model to remove between-subject variance of no interest. A weighted least squares estimation procedure was used to correct for inhomogeneity of covariance across within-group conditions and inhomogeneity of variance across groups.

The SPMs for main effects across groups were masked exclusively with the SPMs for all relevant interactions, using a liberal uncorrected threshold of $p < .05$ for the masks in order to restrict memory effects to those "common" (i.e., similar size) across groups and conditions. This ensures that supposed "common" effects do not in fact represent regions in which groups or conditions actually interact. To correct for multiple comparisons, all results were thresholded at $p < .001$ with a cluster extent of 17, which yielded whole-brain results corrected for multiple comparisons at $p < .05$. We derived this threshold via Monte Carlo simulations to correct for Type I and Type II errors (Slotnick, Moo, Segal, & Hart, 2003).[1] Further, all effects were confirmed via inclusive masking ($p < .01$) with each side of the effect (i.e., young and older adult effects) in order to elucidate the source of interactions in a given contrast (e.g., young > old: integrative > non-integrative), allowing us to determine whether an effect was driven by a group crossover, or whether an effect was in fact larger in one group than another, as well as to ensure that main effects across groups were reliable for each group.

2.6.2.5 ROI Analyses

[1] Our XYZ matrix dimensions were 68 × 68 × 37, with a 3 × 3 × 3.5 mm voxel size resampled to 3 × 3 × 3 mm. The Gaussian full-width half-maximum was set to 15, which was the most conservative (highest) value computed using the t-statistic maps associated with the contrasts of interest. 1000 simulations were run.

ROI analyses were performed using Marsbar (http://marsbar.sourceforge.net). Anatomical template regions for left and right hippocampus were obtained from the Anatomical Automatic Labeling repository (Tzourio-Mazoyer et al., 2002), included with the Marsbar distribution. ROIs were created as 10-mm spheres around specific coordinates from a previous study that investigated semantic relational memory (Prince, Daselaar, & Cabeza, 2005). This study provided coordinates for the left hemisphere locations of VLPFC (BA 45; MNI x, y, z: -50, 37, -12), DLPFC (BA 9/46; -49, 29, 27), and RLPFC (BA 10; -30, 56, -10). To obtain comparable ROIs on the left and right sides, right hemisphere ROIs were constructed as mirror images of those on the left. These ROIs are displayed in Figure 3. The mean signal across all voxels in a defined region was submitted to the GLM analysis described above to produce ROI parameter estimates for each experimental condition for each subject. To examine the contributions to relational integration of these four regions (VLPFC, DLPFC, RLPFC, and Hippocampus), and to probe for hemispheric differences, parameter estimates from each region were submitted to separate repeated measures ANOVAs in SPSS. Left and right hemisphere locations of each ROI were submitted to the same model (Wendelken et al., 2012; Wright, Matlen, Baym, Ferrer, & Bunge, 2007). To correct for multiple comparisons, alpha-values were Bonferroni corrected for the four ROI ANOVA models that were run.

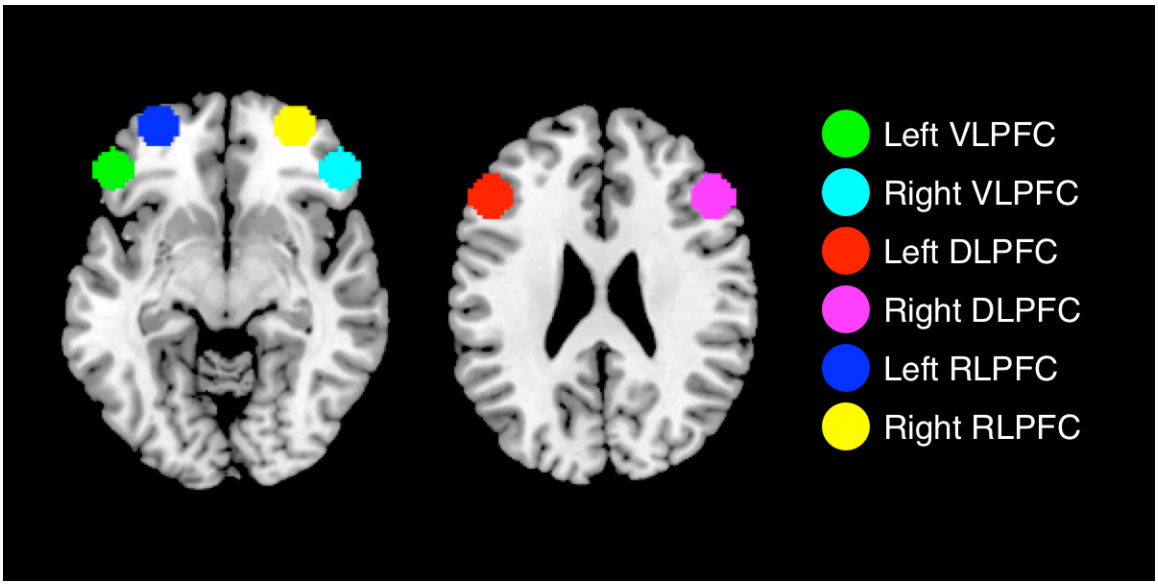

Figure 3 Frontal anatomically defined regions used in ROI analyses

CHAPTER 3. RESULTS

3.1 Post-Scan Questionnaire Responses

Responses to some or all of the survey questions were missing for a few participants. Of those who provided responses, 78.6% (26 of 29 young adults, 18 of 27 older adults) indicated they were visualizing the scene at least some of the time, and 45.5% (15 of 29 young, 10 of 26 old) indicated they were coming up with their own scenes for at least some of the non-integrative trials.

3.2 WAIS Subtest

Group characteristics and results for the WAIS subtests are shown in Table 1. 93.55% of young and 86.67% of older adults had age-corrected scores that fell within two standard deviations of the mean. Two young and four older adults fell three standard deviations above the mean. These results indicate that our sample consisted of high-performing individuals. Young adults performed marginally better than older adults on Similarities [$t(59) = 1.88$, $p = .066$, $d = 0.48$] but the groups had equivalent performance on Visual Puzzles [$t(59) = 0.02$, $p = .985$, $d = 0.003$]. Performance on the WAIS tasks correlated significantly with subsequent memory accuracy for the pairs for both young [$r = .42$, $p = .018$] and older adults [$r = .50$, $p = .005$]. WAIS task performance also correlated significantly with integrative context memory accuracy for young adults [$r = .53$, $p = .002$] but not older adults [$r = .02$, $p = .930$]. This suggests some degree of overlap in processes between our encoding task and the WAIS tasks: young adults may have been utilizing similar integration processes to effectively encode the pair with the context. Older adults,

however, may not have applied these integration strategies to the encoding task, or perhaps applied them less efficiently, which may have contributed to their impaired context memory performance.

3.3 Reasoning Task

Accuracy was calculated for the analogy and semantic conditions as [correct trials/(correct + incorrect trials)]. Only trials with the correct number of responses (i.e., one for analogy, two for semantic) were included in the accuracy calculation; trials with an incorrect number of responses were thrown out. Mean accuracy estimates for analogy and semantic conditions were .76 (SEM = 0.02) and .86 (0.03), respectively, for young adults, and .74 (0.03) and .81 (0.03) for older adults. A Condition (analogy, semantic) x Group (young, old) ANOVA revealed only a main effect of condition [$F(1,44) = 20.00$, $p < .001$, $\eta^2 = 0.31$], indicating higher performance on semantic trials for both age groups. Neither the group main effect nor the Task x Group interaction was significant [Fs < 1.47, ps > .232, η^2s < 0.03].

3.4 Encoding Response Agreement

All participants provided encoding responses that were in line with the intended responses on at least 65% of trials – young adults ranged from 73-96% and older adults from 65-91%. Both groups' agreement was significantly above chance (i.e., 50%), overall and for each encoding condition [young: $t(30)$s > 21.15, ps < .001, ds > 3.80; old: $t(29)$s > 15.15, ps < .001, ds > 2.77]. Agreement was higher for non-integrative than integrative trials [$F(1,59) = 133.20$, $p < .001$, $\eta^2 = 0.69$], and for young adults relative to older adults [$F(1,59) = 13.06$, $p = .001$, $\eta^2 = 0.18$].

3.5 Behavioral Results

3.5.1 Response Times

Mean response times (RTs) for integrative and non-integrative intact pairs are presented in Table 2. A Trial Type (integrative, non-integrative) x Accuracy (hit, miss) x Group (young, old) ANOVA revealed a significant main effect of group [$F(1,59) = 45.14$, $p < .001$, $\eta^2 = 0.43$] and an Accuracy x Group interaction [$F(1,59) = 4.32$, $p = .042$, $\eta^2 = 0.07$]; the main effect of accuracy was marginal [$F(1,59) = 3.35$, $p = .072$, $\eta^2 = 0.05$], as was the Condition x Group interaction [$F(1,59) = 3.58$, $p = .063$, $\eta^2 = 0.06$]. Follow-up ANOVAs for each age group revealed a significant effect of accuracy for older adults [$F(1,29) = 6.20$, $p = .019$, $\eta^2 = 0.18$]; no other effects were significant [Fs < 2.10, ps > .158, η^2s < 0.07], nor were any of the effects for young adults [Fs < 1.48, ps > .234, η^2s < 0.05]. While older adults were generally slower to respond relative to young adults, their responses to trials that were subsequently missed were particularly slow. Slower responses could indicate less efficient encoding processes, which negatively impacted subsequent memory.

An additional Condition (integrative, non-integrative) x Response (likely, unlikely) x Group (young, old) ANOVA assessed RT differences just for the subsequent hits. This revealed significant main effects of condition [$F(1,51) = 5.922$, $p = .018$, $\eta^2 = 0.10$], response [$F(1,51) = 39.59$, $p < .001$, $\eta^2 = 0.44$], and group [$F(1,51) = 46.96$, $p < .001$, $\eta^2 = 0.48$], as well as interactions between condition and group [$F(1,51) = 8.10$, $p = .006$, $\eta^2 = 0.14$] and response and group [$F(1,51) = 6.36$, $p = .015$, $\eta^2 = 0.11$]; Condition x Response and Condition x Response x Group interactions were marginal [$F(1,51) = 3.32$, $p = .075$,

η^2 = 0.06 and $F(1,59) = 3.39$, $p = .071$, $\eta^2 = 0.06$, respectively]. Follow-up analyses for each group revealed significant effects of condition [$F(1,25) = 9.14$, $p = .006$, $\eta^2 = 0.27$], response [$F(1,25) = 27.24$, $p < .001$, $\eta^2 = 0.52$], and a Condition x Response interaction [$F(1,25) = 4.30$, $p = .049$, $\eta^2 = 0.15$] for older adults; only the main effect of response was significant for young adults [$F(1,26) = 11.76$, $p = .002$, $\eta^2 = 0.31$]. For both groups, unlikely interaction judgments were associated with slower RTs than likely judgments. Older adults were particularly slow for non-integrative unlikely judgements. This could indicate that the presence of a scene for the integrative trials facilitated these unlikely judgments by allowing participants to more easily picture the occupation and object in that particular environment; without a scene, participants may have experienced greater difficulty as a result of lacking an anchor for the mental imagery operations utilized for integrative trials.

Table 2 Mean encoding RTs by subsequent pair memory and likeliness response (subsequent pair hits only)

		Young		Old	
		Integrative	Non-Integrative	Integrative	Non-Integrative
Pair Accuracy	Hit	2.00 (0.06)	1.97 (0.06)	2.48 (0.06)	2.57 (0.06)
	Miss	2.00 (0.07)	1.94 (0.10)	2.62 (0.06)	2.70 (0.10)
Encoding Response	Likely	1.95 (0.06)	1.92 (0.07)	2.44 (0.07)	2.54 (0.06)
	Unlikely	2.12 (0.06)	2.14 (0.11)	2.69 (0.08)	3.13 (0.14)

Note. RTs presented in seconds; Standard error of the mean in parentheses.

3.5.2 Pair Memory

Mean proportions of hits, misses, correct rejections (CRs), and false alarms (FAs) for integrative and non-integrative trials are presented in Table 3. Occupation-object pair

accuracy was estimated using *d'* (Stanislaw & Todorov, 1999), calculated separately for integrative and non-integrative trials. Mean *d'* estimates are displayed in Figure 4. To examine pair memory accuracy, these *d'* estimates were entered into an ANOVA with factors of condition (integrative, non-integrative) and group (young, old); this revealed only a main effect of group [$F(1,59) = 9.41$, $p = .003$, $\eta^2 = 0.14$], indicating young adults outperformed older adults. The main effect of condition was not significant, nor was the Condition x Group interaction [Fs < 1]. Thus, the encoding manipulation did not appear to affect memory for the pairs.

Table 3 Mean proportions of integrative and non-integrative hits and misses for intact pairs, and correct rejections and false alarms for rearranged pairs

		Young		Old	
		Integrative	Non-Integrative	Integrative	Non-Integrative
Intact	Hit	0.77 (0.02)	0.75 (0.03)	0.73 (0.02)	0.72 (0.03)
	Miss	0.23 (0.02)	0.25 (0.03)	0.27 (0.02)	0.28 (0.03)
Rearranged	CR	0.91 (0.01)	0.91 (0.02)	0.84 (0.03)	0.83 (0.03)
	FA	0.09 (0.01)	0.09 (0.02)	0.16 (0.03)	0.17 (0.03)

Note. Standard error of the mean in parentheses.

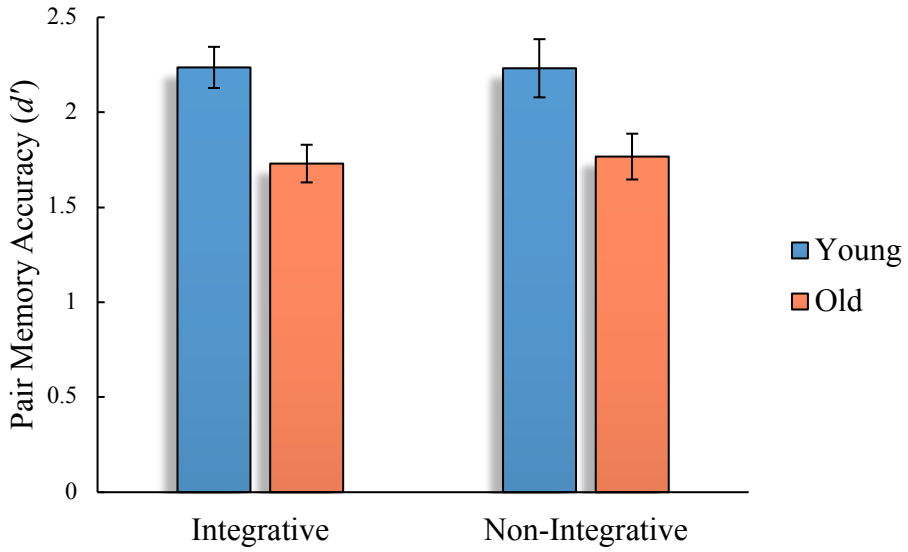

Figure 4 Mean d' estimates for integrative and non-integrative pair memory for young and older adults. Error bars represent the standard error of the mean

3.5.3 Context Memory

Context memory accuracy was assessed using measures of signal detection theory (Stanislaw & Todorov, 1999): response bias (*c*) was calculated for the first context question to estimate the general tendency to select the scene or placeholder option, and *d'* was used to estimate accuracy in selecting the correct scene from the two options for the second context question (integrative trials only). For the purpose of the calculations, in the first context question, a hit is defined as selecting *scene* when the pair was studied as an integrative trial, and a false alarm is defined as selecting *scene* when the pair was studied as a non-integrative trial. Deviations from the neutral point (i.e., when $c = 0$) are measured in standard deviation units. Negative values of *c* indicate bias toward selecting *scene* and positive values indicate bias toward selecting the placeholder option. In the second context question, a hit is defined as selecting the correct scene when it appears as the first of the two options, and a false alarm is defined as incorrectly selecting the first scene option when

the second option was correct. More positive values of *d'* indicate a greater ability to recognize the correct scene. These two measures are plotted against one another, separately for young and older adults, in Figure 5.

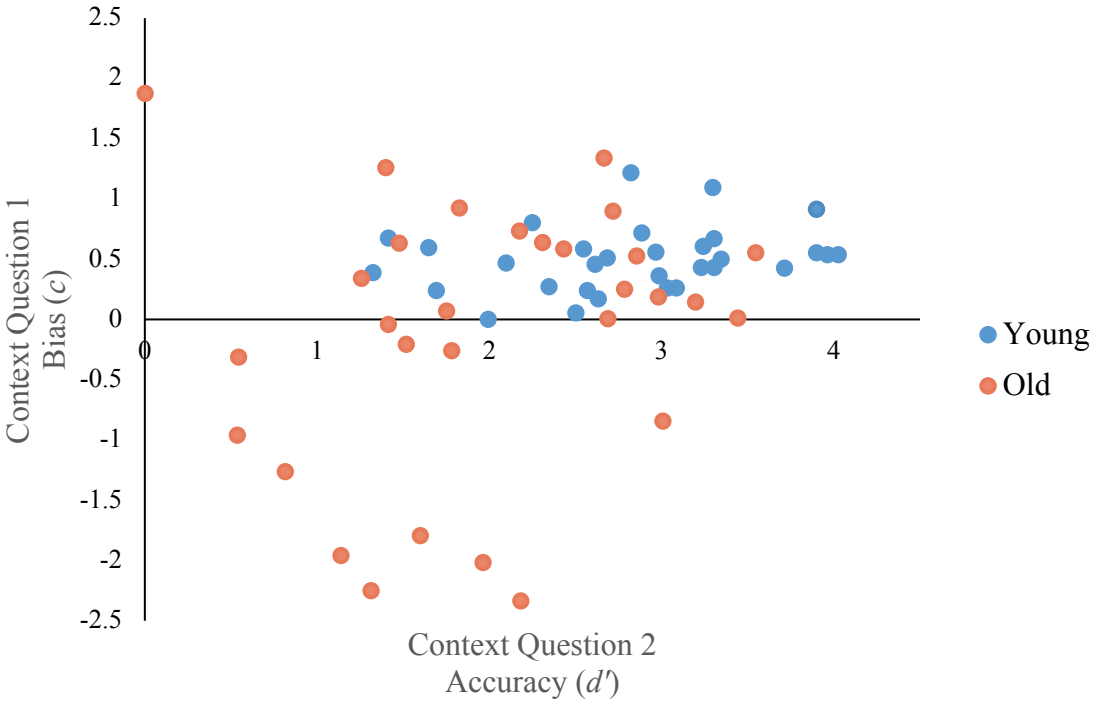

Figure 5 Estimates of response bias (c) for the first context memory question vs. specific scene memory accuracy (d') for the second context memory question

To compare response bias between groups, the absolute value of *c* was used in an independent groups *t*-test, which found that older adults exhibited greater overall response bias [young: $M = 0.50$ ($SD = 0.27$), old: 0.84 (0.72); $t(36.81) = 2.42$, $p = .021$, $d = 1.45$]. As can be seen in the figure, one older adult was an outlier due to the fact that they never selected *scene* for the first question; therefore *d'* could not be calculated, as the second question with the specific scene options was never presented. Young adults demonstrated better context memory overall compared to older adults, as evidenced by their greater *d'*

estimates for both the first, general context question [not displayed in the figure; young: M = 1.37 (SD = 0.87), old: 0.37 (0.55); $t(50.81) = 5.38$, $p < .001$, $d = 1.37$], and the second, specific scene question [young: M = 2.82 (SD = 0.74), old: 2.04 (0.84); $t(58) = 3.78$, $p < .001$, $d = 1.15$].

3.5.4 Likeliness Response

To examine the effects of likeliness responses at encoding on subsequent memory for the pairs, *d'* was calculated and entered into a Condition (integrative, non-integrative) x Response (likely, unlikely) x Group (young, old) ANOVA. This revealed main effects of response [$F(1,59) = 165.78$, $p < .001$, $\eta^2 = 0.74$] and group [$F(1,59) = 8.25$, $p = .006$, $\eta^2 = 0.12$], as well as a Condition x Response interaction [$F(1,59) = 6.97$, $p = .011$, $\eta^2 = 0.11$]; the main effect of condition was marginal [$F(1,59) = 3.62$, $p = .062$, $\eta^2 = 0.06$]. None of the interactions with group were significant [Fs < 1].

Follow-up analyses for each condition revealed main effects of response [$F(1,59) = 121.31$, $p < .001$, $\eta^2 = 0.67$] and group [$F(1,59) = 11.37$, $p = .001$, $\eta^2 = 0.16$] but no interaction between these factors [$F < 1$] for integrative trials. Similarly, for non-integrative, main effects of response [$F(1,59) = 114.32$, $p < .001$, $\eta^2 = 0.66$] and group [$F(1,59) = 4.47$, $p = .039$, $\eta^2 = 0.07$] were significant, but not the interaction [$F < 1$]. Parallel follow-up analyses were conducted for each likeliness response. This revealed main effects of condition [$F(1,59) = 11.67$, $p = .001$, $\eta^2 = 0.17$] and group [$F(1,59) = 6.21$, $p = .016$, $\eta^2 = 0.10$] but no interaction between these factors [$F < 1$] for likely responses. For unlikely responses, only the main effect of group was significant [$F(1,59) = 6.70$, $p = .012$, $\eta^2 = 0.10$], not the main effect of condition nor the interaction [Fs < 1].

These results suggest that when making a judgment about item relationships that are consistent with one's prior knowledge, this consistency can facilitate successful encoding and subsequent retrieval. Here, it appears that both young and older adults were able to leverage this knowledge to improve memory for the occupation-object pairs, for both integrative and non-integrative trials. Figure 6 displays the *d'* estimates.

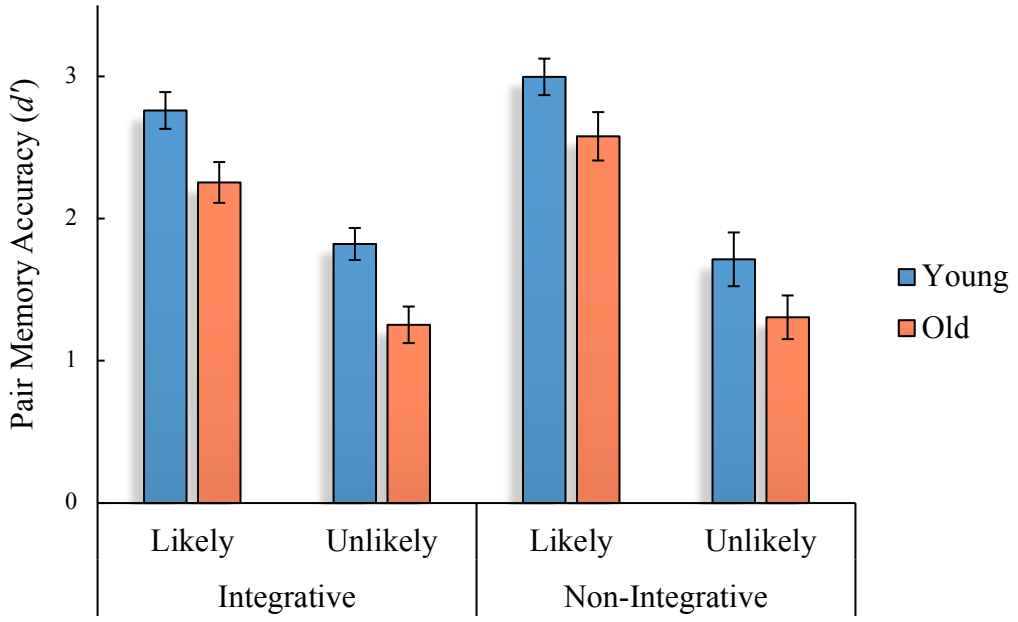

Figure 6 Estimates of pair memory accuracy (*d'*) as a function of encoding response. Error bars represent standard error of the mean

To determine if this consistency benefit extended to memory for the scenes, context memory accuracy, as measured by proportion of context correct trials, was calculated for integrative pair hits and misses, separated by encoding response. This is shown in Figure 7. To get the context correct, the participant needed to select *scene* for the first question, then select the correct scene from the two options in the second question. Thus, 25% correct would be considered performing at chance. Both groups' context memory was significantly above chance for trials where the pair was also correctly remembered [i.e., pair hits; *t*(30)s

> 6.62, *p*s < .001, *d*s > 1.19 for young adults; *t*(29)s > 2.88, *p*s < .007, *d*s > 0.53 for older adults]. Young adults' context memory performance was just above chance for likely pair misses [$t(29) = 2.10$, $p = .045$, $d = 0.38$], but below chance for unlikely pair misses [$t(30) = -2.32$, $p = .027$, $d = 0.42$]. Older adults were not significantly above chance for pair misses, regardless of encoding response [$t(28) = 1.25$, $p = .221$, $d = 0.23$ for likely, $t(29) = -0.45$, $p = .656$, $d = 0.08$ for unlikely]. Because performance was not above chance for pair misses, context accuracy estimates for pair hits were submitted to a Response (likely, unlikely) x Group (young, old) ANOVA, which revealed main effects of response [$F(1,59) = 21.30$, $p < .001$, $\eta^2 = 0.27$] and group [$F(1,59) = 5.15$, $p = .027$, $\eta^2 = 0.08$], but no interaction between these factors [$F < 1$]. Together, these results suggest that when the judged interaction is consistent with one's prior knowledge, memory for both the pair and the context is improved, relative to judgements that are inconsistent. Young and older adults were able to leverage prior knowledge similarly to support successful encoding and subsequent retrieval.

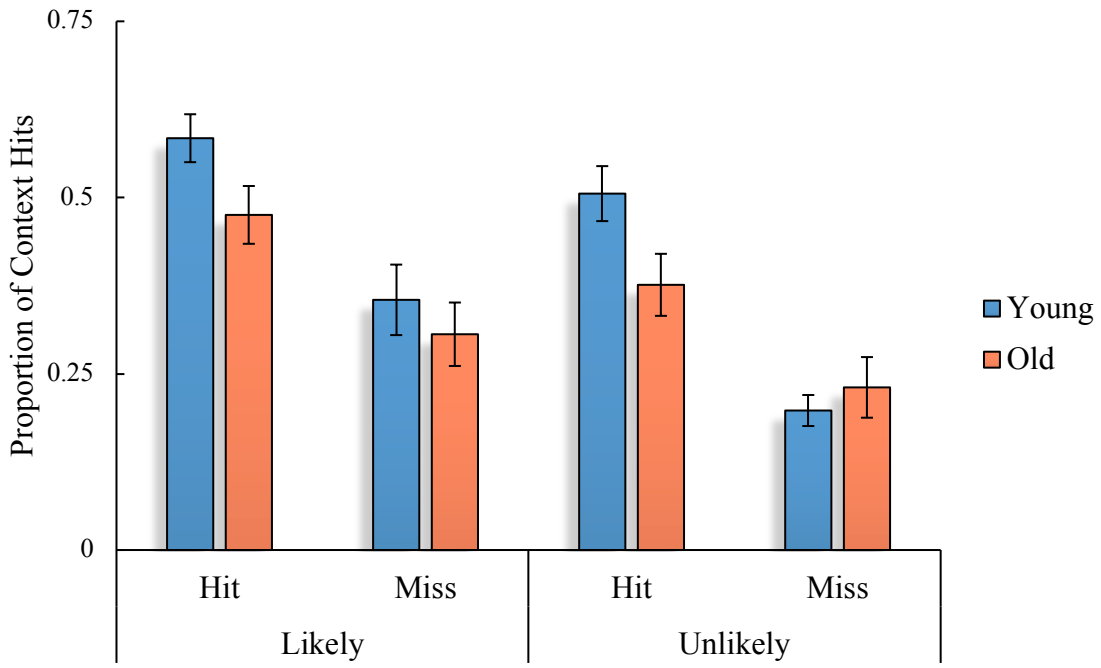

Figure 7 Proportion of integrative trials where both context memory questions were answered correctly, separated by encoding response and pair memory accuracy. Error bars represent standard error of the mean. The dashed line indicates chance performance (.25)

3.6 fMRI Results

3.6.1 ROI Analyses

We first sought to test the hypothesis of the rostral-caudal gradient within the PFC; that is, more caudal regions will show similar activity between encoding tasks (i.e., analogy and semantic, integrative and non-integrative), while more rostral regions show greater activity for the tasks that require higher-order processing (i.e., analogy and integrative). Parameter estimates were extracted from eight anatomically defined ROIs: left and right VLPFC (BA 45), DLPFC (BA 9/46), RLPFC (BA 10), and Hippocampus. We submitted parameter estimates from each region to various ANOVA models to assess reasoning, pair

memory, context memory, and effects of encoding response. A Bonferroni α-value of .0125 was used for all significance tests.

3.6.1.1 Reasoning Task

Due to high performance, a majority of participants had an insufficient number of incorrect trials; therefore, ROI parameter estimates were extracted only for correct trials. A Task (analogy, semantic) x Hemisphere (left, right) x Group (young, old) ANOVA for VLPFC revealed a marginal Task x Hemisphere interaction [$F(1,44) = 6.28$, $p = .016$, $\eta^2 = 0.13$]; however, follow-up analyses did not reveal significant task main effects or interactions in either hemisphere [Fs < 4.35, ps > .043]. No other effects in the omnibus ANOVA were significant [Fs < 1.86, ps > .180]. ANOVAs for DLPFC, RLPFC, and Hippocampus did not reveal any significant task main effects or interactions [Fs < 3.49, ps > .068].

3.6.1.2 Subsequent Memory Effects

Parameter estimates for each region were first submitted to a Condition (integrative, non-integrative) x Pair Accuracy (hit, miss) x Hemisphere (left, right) x Group (young, old) ANOVA. The DLPFC model revealed a significant main effect of condition [$F(1,49) = 7.27$, $p = .010$, $\eta^2 = 0.13$], which was modified by a marginal Condition x Hemisphere interaction [$F(1,49) = 6.60$, $p = .013$, $\eta^2 = 0.12$]. Follow-up analyses indicated left DLPFC was more sensitive to integration demands [integrative > non-integrative; $F(1,49) = 10.39$, $p = .002$, $\eta^2 = 0.18$] than right DLPFC [$F(1,49) = 2.91$, $p = .095$, $\eta^2 = 0.06$]. ANOVAs for

VLPFC, RLPFC, and Hippocampus did not reveal any significant condition or pair accuracy main effects or interactions [Fs < 5.35, ps > .025].

3.6.1.3 Integration Effects

To investigate sensitivity to increasing integration demands, parameter estimates for each ROI were submitted to a Condition (integrative pair + context, integrative pair – context, non-integrative pair hit) x Hemisphere (left, right) x Group (young, old) ANOVA. The DLPFC model revealed a significant main effect of condition [$F(2,112) = 10.17$, $p < .001$, $\eta^2 = 0.15$], which was modified by an interaction with hemisphere [$F(2,112) = 7.39$, $p = .001$, $\eta^2 = 0.12$]. Follow-up analyses for each hemisphere indicated that the condition effect was reliable in both hemispheres, though more significantly in left DLPFC [$F(2,112) = 13.46$, $p < .001$, $\eta^2 = 0.19$] than in right DLPFC [$F(2,112) = 5.02$, $p = .008$, $\eta^2 = 0.08$]. Pairwise comparisons between each condition revealed that in the left hemisphere, integrative pair + context elicited significantly more DLPFC activity than integrative pair – context [$t(57) = 3.71$, $p < .001$] and non-integrative pair hits [$t(57) = 4.83$, $p < .001$]; the difference between integrative pair – context and non-integrative pair hits was not significant [$t(57) = 1.40$, $p = .169$]. In the right hemisphere, integrative pair + context elicited significantly more DLPFC activity than non-integrative pair hits [$t(57) = 2.87$, $p = .006$] but only marginally more activity than integrative pair – context [$t(57) = 2.41$, $p = .019$]; the difference between integrative pair – context and non-integrative pair hits was not significant [$t(57) = 0.52$, $p = .608$]. No other condition main effects or interactions were significant in the omnibus DLPFC ANOVA nor any of the follow-up tests [Fs < 1]. Results

can be seen in Figure 8. ANOVAs for VLPFC, RLPFC, and Hippocampus did not reveal any significant Condition effects or interactions [Fs < 2.72, ps > .070].

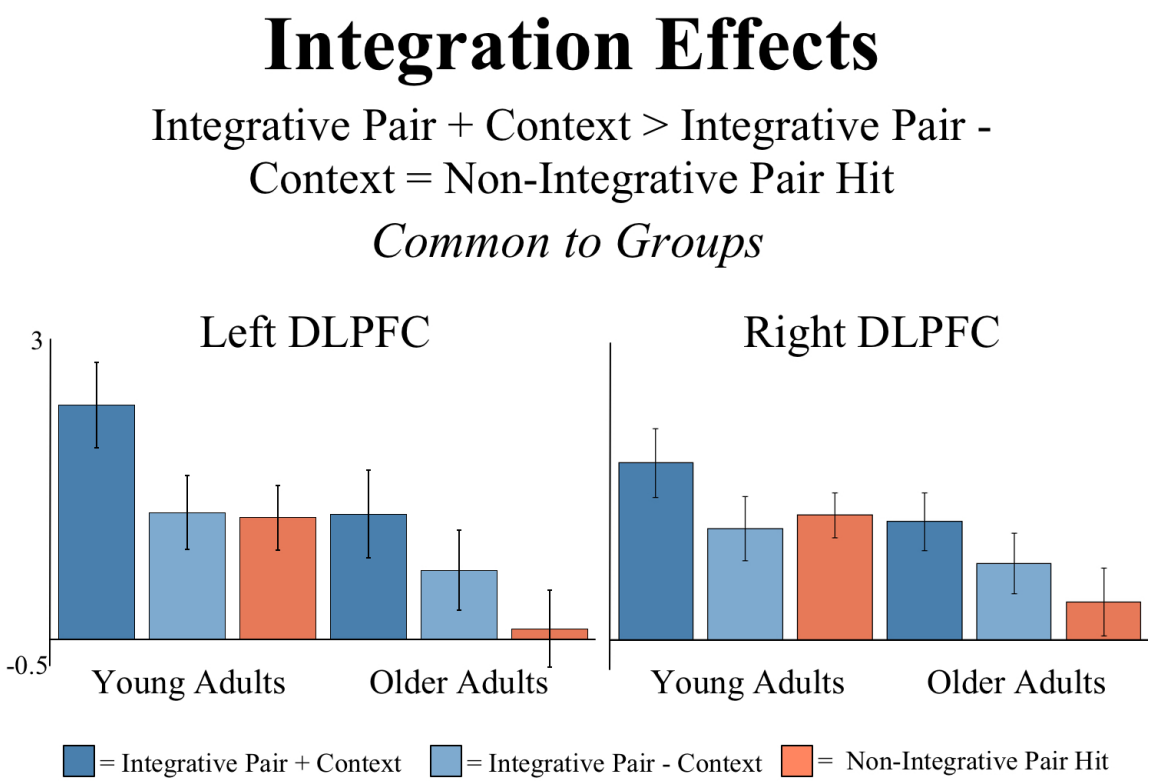

Figure 8 Integration effects at encoding for bilateral DLPFC ROIs. Plots show parameter estimates for integrative pair and context hits, integrative pair hits and context misses, and non-integrative pair hits. Error bars depict standard error of the mean across participants for each group

3.6.1.4 Likeliness Effects

Parameter estimates from each ROI were submitted to a Condition (integrative, non-integrative) x Response (likely, unlikely) x Hemisphere (left, right) x Group (young, old) ANOVA. The model for VLPFC revealed a marginal effect of response [$F(1,47)$ = 6.67, p = .013, η^2 = 0.12], which was modified by an interaction with hemisphere [$F(1,47)$ = 21.18, p < .001, η^2 = 0.31]. Follow-up analyses for each hemisphere indicated the effect

was significant in left VLPFC [$F(1,47) = 15.23$, $p < .001$, $\eta^2 = 0.25$], but not right [$F(1,47) = 0.13$, $p = .716$, $\eta^2 = 0.003$].

The DLPFC ANOVA revealed significant main effects of condition [$F(1,47) = 12.55$, $p = .001$, $\eta^2 = 0.21$] and response [$F(1,47) = 8.38$, $p = .006$, $\eta^2 = 0.15$], the latter of which was modified by a marginal interaction with hemisphere [$F(1,47) = 6.19$, $p = .016$, $\eta^2 = 0.12$]. Follow-up analyses for each hemisphere revealed that only the condition effect was significant in the right hemisphere [$F(1,47) = 7.80$, $p = .008$, $\eta^2 = 0.14$], showing integrative > non-integrative; in left DLPFC, both the effects of condition [$F(1,47) = 14.26$, $p < .001$, $\eta^2 = 0.23$] and response [$F(1,47) = 12.97$, $p = .001$, $\eta^2 = 0.22$] remained significant, with integrative > non-integrative and likely > unlikely.

The model for RLPFC revealed only a significant main effect of response [$F(1,47) = 28.05$, $p < .001$, $\eta^2 = 0.37$], showing likely > unlikely. Finally, the Hippocampus ANOVA revealed a significant main effect of response [$F(1,47) = 7.80$, $p = .008$, $\eta^2 = 0.14$], as well as a Condition x Response x Hemisphere interaction [$F(1,47) = 8.28$, $p = .006$, $\eta^2 = 0.15$]. Follow-up analyses for each hemisphere revealed the effect of response was significant bilaterally [left: $F(1,47) = 7.08$, $p = .011$, $\eta^2 = 0.13$; right: $F(1,47) = 6.79$, $p = .012$, $\eta^2 = 0.13$]. No other effects were significant in the omnibus ANOVA [Fs < 3.76, ps > .059] or follow-up analyses [Fs < 4.18, ps > .047].

3.6.2 Whole-Brain Analyses

Though we were mainly interested in the specific regions covered in the ROI analyses, we also conducted whole brain analyses to determine other regions sensitive to our effects of interest.

3.6.2.1 Reasoning Task

Contrary to our predictions that the analogy task would elicit greater frontal activity than the semantic task, only occipital regions emerged as significant from this contrast. Surprisingly, the semantic task showed greater activation of more anterior lateral PFC areas in left and right hemispheres, though these clusters were relatively small. No age differences were observed in either contrast. These regions are shown in Table 4 for both contrasts.

Table 4 Peak coordinates for whole-brain comparisons of the reasoning task

Region	*L/R*	*BA*	*x, y, z*	*t-score*	*Cluster size*
Across Groups: Analogy Correct > Semantic Correct					
Middle Occipital Gyrus	L	19	-30, -82, 20	5.49	128
Primary/Secondary Visual Cortex	L	17/18	-15, -94, 2	4.73	23
Middle Occipital Gyrus	R	19	39, -82, 23	4.28	17
Across Groups: Semantic Correct > Analogy Correct					
Precentral Gyrus	L	6	-36, -16, 65	5.98	336
Middle Frontal Gyrus	L	10/46	-27, 50, 11	4.31	18
Dorsolateral Prefrontal Cortex	R	9/46	42, 35, 38	4.11	19
Insula	R	13	60, -37, 20	3.88	20

Given our particular interest in determining whether the most anterior aspects of the PFC were sensitive to integration demands, we reanalysed these contrasts at a reduced threshold ($p < .005$). This revealed a small cluster in left medial frontopolar cortex (BA 10) that showed greater activity for analogy than semantic (Figure 9). Together, these results may suggest a functional dissociation within BA 10.

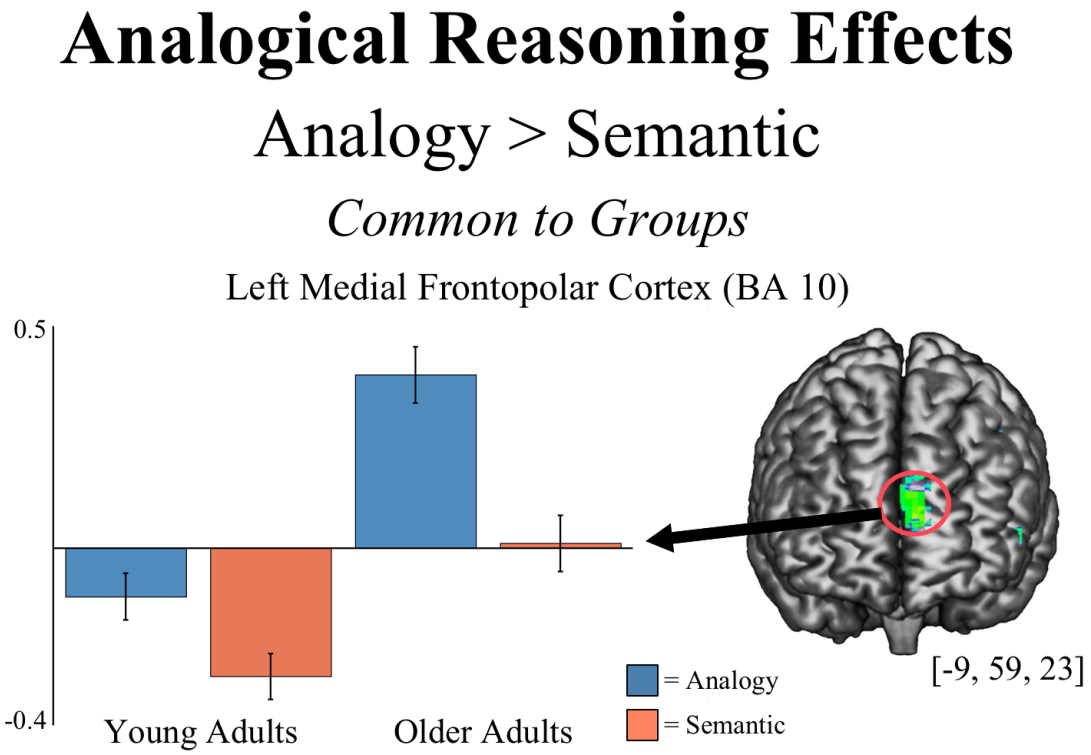

Figure 9 Analogical reasoning effects. Analogy > Semantic (correct trials only) effects for the left medial frontopolar cortex (BA 10; cluster size = 65 voxels, peak voxel at [-9, 59, 23], $t = 4.04$) are displayed on an MNI reference brain. The plot shows parameter estimates for analogy correct and semantic correct trials for both groups. Error bars depict standard error of the mean across participants for each group [p < .005, uncorrected, with a 17 voxel extent; exclusive masking conducted as described in fMRI analysis section].

3.6.2.2 Subsequent Memory Effects

Two regions emerged as significant from the interaction contrast between condition and subsequent memory, across groups, shown in Table 5. Further investigation of this interaction revealed that activity in the right superior/middle frontal gyrus was driven by a crossover effect: subsequent remembering (hit > miss) for integrative and subsequent forgetting (miss > hit) for non-integrative. Activity in the occipital region was reliable only for integrative hit > miss. No regions showed significant interactions with age. While it is somewhat surprising that subsequent memory effects did not follow the typical pattern of encoding activity (e.g., greater MTL activity for hits than misses), participants in this study were generally high performing. Therefore, this contrast was likely underpowered as a result of low trial counts for misses.

Table 5 Peak coordinates for regions showing subsequent memory effects

Region	*L/R*	*BA*	*x, y, z*	*t-score*	*Cluster size*
Across Groups: Hit > Miss, Integrative > Non-Integrative					
Superior/Middle Frontal Gyrus	R	6/8	24, 14, 59	4.59	98
Middle Occipital Gyrus	L	18	-9, -100, 11	4.35	41

3.6.2.3 Integration Effects

Integration effects were analysed first by comparing high and low integration demands (integrative pair hit, regardless of context accuracy > non-integrative pair hit). Several regions showed greater effects for integrative compared to non-integrative pair hits, shown in the top portion of Table 6. These regions included large bilateral clusters in the occipital cortex and retrosplenial cortex, left inferior frontal gyrus, and left superior and

inferior parietal cortices. Relative to the young, older adults showed greater activity in the left middle occipital gyrus for this contrast.

Next, to analyse integration demands in terms of successfully integrating the context with the pair, integrative trials where both the pair and context were subsequently remembered were compared to trials where only the pair was remembered (integrative pair + context > integrative pair – context). These results are shown in the lower portion of Table 6. Across groups, integrative pair + context showed greater activity than integrative pair – context in left DLPFC (BA 9 and 46), consistent with the findings of the ROI analyses. One region in left anterior VLPFC (BA 47) showed greater integration effects for the young than the old. While our ROI results did not reflect this age effect, the VLPFC ROI was located more posteriorly, centered in BA 45, and therefore may not have detected the activity in this more anterior region. No regions showed greater integration effects for the old than the young.

Table 6 Peak coordinates for regions showing integration demand differences

Region	*L/R*	*BA*	*x, y, z*	*t-score*	*Cluster size*
Across Groups: Integrative Pair +/- Context > Non-Integrative Pair Hit					
Middle Occipital Gyrus	L	18	-15, -94, 2	8.16	930
Primary Visual Cortex	*R*	*17*	*18, -94, 2*	*7.48*	
Retrosplenial Cortex	R	30	3, -58, 14	5.62	385
	L	*30*	*-9, -55, 14*	*5.03*	
Inferior Frontal Gyrus	L	44	-45, 17, 26	5.54	406
Superior Frontal Gyrus	L	6	-6, 8, 56	4.19	94
Inferior Parietal Cortex	L	7	-30, -58, 41	4.16	110
Superior Parietal Cortex	*L*	*7*	*-27, -58, 50*	*3.91*	

Table 6 continued

Middle Temporal Gyrus	L	21	-54, -37, 2	3.82	20
Old > Young: Integrative Pair +/- Context > Non-Integrative Pair Hit					
Middle Occipital Gyrus	L	19	-45, -79, 17	3.75	24
Across Groups: Integrative Pair + Context > Integrative Pair - Context					
Dorsolateral Prefrontal Cortex	L	9	-30, 14, 47	4.65	64
Dorsolateral Prefrontal Cortex	L	46	-42, 17, 29	4.24	181
Young > Old: Integrative Pair + Context > Integrative Pair - Context					
Anterior Ventrolateral Prefrontal Cortex	L	47	-24, 41, 5	3.76	17

Note. Italicized regions are included to highlight additional areas showing significant activation within the same cluster.

3.6.2.4 Effects of Likeliness on Integration Demands

Likeliness response effects (likely > unlikely), across groups and conditions, were masked inclusively ($p < .01$) with the integration demands contrasts to identify regions that showed integration effects *and* likeliness effects. These results are shown in **Error! R eference source not found.**. Regions that showed greater activity for integrative than non-integrative, and greater activity for likely than unlikely, included left inferior and superior parietal cortices, bilateral retrosplenial cortex, and left middle frontal gyrus. DLPFC (BA 9) and mid-VLPFC (BA 45) showed greater activity for both successful integration (integrative pair + context > integrative pair – context) and likeliness effects. No regions showed significant interactions with age. Overlap between these contrasts suggests that the regions sensitive to likeliness, or prior knowledge consistency effects, also support integration and context memory accuracy.

Table 7 Peak coordinates for regions showing likeliness effects (likely > unlikely) inclusively masked with integration demand contrasts

Region	*L/R*	*BA*	*x, y, z*	*t-score*	*Cluster size*
Across Groups: Likely Hit > Unlikely Hit					
Masked with Integrative Pair +/- Context > Non-Integrative Pair Hit					
Inferior Parietal Cortex	L	40	-36, -52, 50	5.66	84
Superior Parietal Cortex	*L*	*7*	*-33, -61, 53*	*5.46*	
Retrosplenial Cortex	R	30	6, -52, 17	4.15	75
	L	*30*	*-6, -58, 20*	*3.94*	
Middle Frontal Gyrus	L	6	-45, 8, 44	4.13	34
Masked with Integrative Pair + Context > Integrative Pair - Context					
Dorsolateral Prefrontal Cortex	L	9	-42, 11, 44	4.50	40
Ventrolateral Prefrontal Cortex	L	45	-51, 17, 8	3.91	21

Note. Italicized regions are included to highlight additional areas showing significant activation within the same cluster.

CHAPTER 4. DISCUSSION

The present study investigated the effects of aging on relational integration in associative encoding. We were particularly interested in assessing the hypothesized rostral-caudal axis of PFC organization and how aging affects recruitment of regions along this hierarchical gradient. As predicted, young adults outperformed older adults in memory for both the occupation-object pairs and their associated contexts. However, there was no interaction between age and level of integration; both young and older adults demonstrated similar memory for integrative and non-integrative pairs. Imaging results showed that, across groups, the highest integration demands (integrative pair and context hits > context misses) elicited increased recruitment of left DLPFC (BA 9/46), but not VLPFC (BA 44/45), consistent with models of hierarchical organization along the rostral-caudal axis. These results and their implications are discussed below.

4.1 Behavioral Results

4.1.1 Pair and Context Memory

In line with previous findings from our lab (Duarte et al., 2008; Dulas & Duarte, 2012, 2014) and others (Glisky, Rubin, & Davidson, 2001; Mitchell & Johnson, 2009; Naveh-Benjamin, 2000), older adults exhibited impaired memory performance for the occupation-object pairs, as well as the scene contexts with which the pairs were studied. While we predicted that only young adults would show equivalent memory for the integrative and non-integrative pairs, both groups exhibited this equivalency, suggesting the encoding manipulation did not affect subsequent memory for the pairs in either group.

We speculated that older adults may remember fewer of the trials that placed additional demands on integration processes, but this did not seem to be the case. Nevertheless, we do not believe this should be taken to suggest the older adults were performing the encoding task as optimally as the young. For one, young adults tended to have higher agreement with the intended responses relative to older adults. Further, looking at agreement for each condition, both groups showed significant correlations between agreement on non-integrative trials and subsequent pair memory accuracy [r = .54, p = .001 and r = .42, p = .010, respectively]. However, only young adults showed significant correlations between agreement on integrative trials and subsequent pair [r = .49, p = .003] and context [r = .84, p = .003] memory accuracy; these correlations for older adults were not significant [r = -.01, p = .477 and r = .17, p = .184, respectively]. It could be that older adults were not integrating the pair with the context, which would lower their agreement with the intended responses on those trials where the scene is critical to the decision (i.e., the trials where the occupation and object would likely interact, but not within the context of the given scene). The fact that older adults showed a significant correlation between agreement on non-integrative, but not integrative, trials and memory accuracy suggests integration processes could have been impaired, or at least inefficient in this age group.

Figure 5 supports the possibility of inefficient integration processes in older adults: not only was their context memory accuracy lower than that of young adults for both the general and specific context questions, they also demonstrated greater overall bias. While young adults showed slight bias toward selecting the placeholder option (all but two fell within one standard deviation of the neutral point), the positive, though relatively weak, correlation between bias (c) on the first question and accuracy (d') on the second (r = .25)

could indicate a strategy where the scene option was only chosen when the participant had a certain level of confidence in their response; if confidence was low, they may have selected the placeholder option so as to avoid being confronted with the forced-choice decision in the second question. Unfortunately, we did not directly measure confidence in this design; this should be a consideration for future studies.

Older adults, on the other hand, showed greater response bias in both directions. Those who exhibited positive bias showed the opposite trend of the young (r = .34); that is, lower response bias on the first question was associated with better memory for the specific scene in the second question. For the older adults who showed a tendency to select scene for the first question (i.e., negative response bias), the correlation between bias and accuracy was relatively weak (r = .16). While it remains an open question whether some sort of strategy was leveraged by the young adults, their improved accuracy relative to older adults suggests greater efficiency in task performance. It should be noted however that few age differences emerged from the imaging results. It is therefore possible that age-related differences in context memory emerged as a result of inefficient retrieval, as opposed to encoding, processes. This is something that would need to be investigated in future studies. An alternative, though not mutually exclusive, possibility is that the univariate approach to fMRI analyses was not sensitive to these age differences. Our next step will be to investigate this possibility using a multivariate approach, as discussed below.

4.1.2 Prior Knowledge Consistency Benefit

Though the effect of likeliness responses on subsequent memory was not an initial focus of this study, previous research has shown memory benefits for material that is

relatable to, or consistent with, existing knowledge (Anderson, 1981; Brod, Lindenberger, Werkle-Bergner, & Shing, 2015; DeWitt, Knight, Hicks, & Ball, 2012; see Gilboa & Marlatte, 2017 for review). This knowledge is represented by schemas in long-term memory, which serve as general-form reference templates that influence how new information is perceived and remembered (Ghosh & Gilboa, 2014). The marked difference in memory for trials judged as likely versus unlikely in the present study supports this idea of a schema memory benefit. Participants' prior knowledge of the various occupations, objects, and scenes they encountered in the study served as the template against which the new associations were compared to make likeliness/congruency judgments. Encoding of these new associations was facilitated by the presence of a congruent schema (Tse et al., 2011).

Non-integrative likely pairs were remembered better than integrative likely pairs, possibly due to greater ease in utilizing schema for these trials. For example, on a non-integrative trial, only one association, between the occupation and object, needed to be matched with an existing schema. However, on integrative trials, the additional relations between items in the pair and the scene may have lowered the overall congruency with one's existing schema, resulting in less efficient encoding of the pair. Older adults may have been particularly impacted by the demands to compare these additional relations, as the largest group difference was found for integrative trials. This suggests that older adults could leverage prior knowledge more like the young when the pair was studied in isolation, but had greater difficulty when the comparison involved additional consideration of the scene.

Previous work has shown that older adults can be more influenced by schematic knowledge than young adults (see Umanath & Marsh, 2014 for review). Age deficits in memory can be mitigated when material is consistent with existing schemas (Castel, 2005; Shi, Tang, & Liu, 2012). Inconsistent material, however, may have a greater detrimental effect on older adults' memory relative to their younger counterparts (Dalla Barba, Attali, & La Corte, 2010). While schema consistency was not enough to overcome age-related memory deficits in the current study, it is plausible that the degree of consistency varied trial to trial, which could not be captured with a simple likely/unlikely decision. A consideration for future studies would be to allow for likeliness judgements to be made on a scale (e.g., *very likely, somewhat likely*; van Kesteren et al., 2013) to better understand how prior knowledge congruency interacts with age to influence relational encoding.

4.2 Imaging Results

4.2.1 Reasoning Task

Previous studies of analogical reasoning have shown that more anterior aspects of the PFC are more active during evaluation of analogies than simple evaluation of individual semantic relations (Bunge et al., 2005; Christoff et al., 2001; Wendelken, Nakhabenko, Donohue, Carter, & Bunge, 2008) Somewhat surprisingly, participants in the current study showed greater activation of lateral anterior areas (e.g., left BA 10/46 and right BA 9/46) for the semantic task compared to the analogy task. However, when the threshold was slightly lowered, a significant cluster in the left medial frontopolar cortex (BA 10) emerged showing greater activity for analogy than semantic. While many studies report recruitment of more lateral anterior regions with increasing relational complexity, medial anterior areas

have also been reported (Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006). Despite the wealth of evidence that reasoning abilities tend to decline with age (Salthouse, 1992; Viskontas et al., 2005), performance was equivalent between groups. This raises the possibility that analogy task demands were not high enough to necessitate recruitment of RLPFC or other lateral aPFC regions (Christoff, Keramatian, Gordon, Smith, & Madler, 2009).

4.2.2 Integration Demands

Given the extensive work that has implicated the RLPFC as critical for relational integration (Bunge et al., 2005; Christoff et al., 2001; Wendelken & Bunge, 2010), we predicted this region would show a pattern of increased recruitment with increasing integration demands. However, our ROI for this region was not found to be sensitive to our experimental manipulations. There are a few possibilities for this. The first is that our integrative condition may not have taxed the highest-level abstraction processes that have been associated with the RLPFC (Badre & D'Esposito, 2007; Christoff & Gabrieli, 2000). For example, Raven's Progressive Matrices and verbal propositional analogy tasks, which show reliable recruitment of more anterior PFC regions with increasing relational complexity, require relational extraction, maintenance, and inference (Christoff et al., 2001; Wendelken et al., 2008). While we predicted that the joint consideration of relations between items in the triad (i.e., the scene-occupation, scene-object, and occupation-object relations) would engage relational integration processes, the lack of an inference component or other increased task demands may have reduced the necessity for recruitment of more anterior regions (Christoff et al., 2009; Krawczyk, Michelle McClelland, & Donovan, 2011). However, we did find DLPFC (BA 9/46) to be sensitive to integration

demands, suggesting at least some extent of hierarchical recruitment of PFC subregions for relational encoding.

Greater activity in parietal, retrosplenial, and visual cortices for integrative relative to non-integrative trials suggests that both young and older adults were using the provided scenes to inform their likeliness judgments, consistent with the majority of participants' questionnaire responses indicating they were visualizing the scene. It has been suggested that the retrosplenial cortex is part of a larger network that supports "scene construction", a process that involves mentally generating and maintaining a scene or event (Hassabis et al., 2009; Hassabis, Kumaran, & Maguire, 2007; Hassabis & Maguire, 2007). Similarly, parietal regions have been shown to actively represent or processes structured mental representations (Crone et al., 2009), and may serve as the foundation for relational representations (Wendelken et al., 2008). Additionally, this contrast showed greater activity in left inferior frontal gyrus (BA 44), an area often associated with "first-order" processes such as selection of item features (Christoff & Gabrieli, 2000) and selection of item representations from memory (Wais et al., 2012).

However, activation of these mental representation regions did not appear to support successful contex encoding. Instead, aPFC regions like left DLPFC were recruited to bind the scene, occupation, and object associations into an integrated memory trace, consistent with evidence that DLPFC is important for processing relationships between items (i.e., "second-order" processes; Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Ranganath & Knight, 2002). Both young and older adults exhibited increased activity in left DLPFC with increasing integration demands, showing the greatest activity for integrative trials where both the pair and context were remembered correctly. This supports

the possibility that more posterior PFC regions are sufficient to encode the details necessary for pair memory, while more anterior regions must be additionally recruited to effectively encode the associated contextual details.

While it is well established that the RLPFC is directly involved in relational retrieval (Bunge et al., 2005; Reynolds et al., 2006; Westphal et al., 2016), its role in relational encoding is less well understood. We predicted that RLPFC may increasingly contribute to episodic encoding as associations between event details become more complex, similar to the hierarchical recruitment observed in relational reasoning tasks. Prince, Daselaar, and Cabeza (2005) found that encoding of simple semantic relations elicited greater left VLPFC activity, while retrieval of those associations elicited greater left DLPFC and RLPFC activity. However, DLPFC is known to play an important role in episodic encoding by contributing to successful organization of associations for long-term memory (Blumenfeld & Ranganath, 2007). Using the peak coordinates for these regions from Prince and colleagues (2005) to define our ROIs, we found that DLPFC was important for successful integration of the additional relations between items in the pair and the scene.

While we did not find increased activity in our most anterior ROI, it is important to note that we limited these analyses to those coordinates from the Prince et al. (2005) study. Exact ROI labelling can be challenging, especially given the lack of precisely defined boundaries for the RLPFC (Wendelken et al., 2008). While there is wide agreement that the area encompasses BA 10, the definition is often broadened to include immediately neighbouring aspects of BAs 9, 46, and 47 (Westphal et al., 2016). Indeed, a number of studies find that regions most sensitive to the highest levels of relational complexity are not limited to BA 10: some find overlap with areas generally associated with the VLPFC

(BA 10/7; Cho et al., 2010; Wendelken et al., 2008) or DLPFC (9/10; Green et al., 2006), while others associate RLPFC solely with BA 46, and define the frontopolar cortex as a separate region encompassing BA 10 (Nee, Jahn, & Brown, 2014). Given the lack of precise boundaries for defining regions, it is feasible that ROI analyses may miss important differences in hierarchical recruitment of PFC subregions.

4.3 Next Steps

Moving forward, we plan to take a multivariate approach to data analysis, as these methods tend to be more sensitive to differences in activation. Unlike univariate approaches, which assess differences in specific brain regions, behavioral partial least squares (B-PLS) analysis is not constrained to sets of voxels that are contiguous; instead, this approach looks at spatial and temporal distributions to identify time-varying distributed patterns of activity that differentiate conditions in the experimental design (McIntosh & Lobaugh, 2004).

B-PLS has a number of advantages that may be particularly important for the current study. For one, in the current univariate analyses, we increased the duration of the epochs in an attempt to better capture the hemodynamic response function (HRF), reasoning that the duration of the peak BOLD response for integration effects would be sustained relative to lower-order inter-item comparison effects. It is possible that this longer duration model was not an optimal fit for all trials or participants, particularly those with shorter response times. B-PLS, unlike univariate, makes no assumptions about the shape of the HRFs. Furthermore, PLS allows for flexible configurations that enable assessment of activation differences, brain-behavior relations, and functional connectivity (McIntosh, Chau, &

Protzner, 2004). We will use B-PLS to identify whole-brain patterns of task-related encoding activity that correlate with pair and context memory accuracy and differ with age. This data-driven approach will circumvent the complications of labeling the imprecisely defined PFC subregions, allowing us to investigate networks of regions involved in relational encoding, and improve our ability to detect group differences to better understand the age-related performance deficits.

4.4 Conclusions

The current study provides evidence of progressively anterior PFC recruitment with increasing integration demands during associative encoding. While posterior PFC regions such as posterior/mid-VLPFC are engaged for "lower-order" processing of item details, additional engagement of more anterior regions such as DLPFC are necessary to bind these details into an integrated memory trace. Despite showing similar recruitment of these regions as young adults, older adults' memory deficits persisted. While this could reflect that their integration processes were simply inefficient, we believe there are likely activation differences that correspond to these memory impairments, which we will investigate using multivariate behavioral PLS.

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